# Combination scaffolds of salmon fibrin, hyaluronic acid, and laminin for human neural stem cell and vascular tissue engineering.

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**Public Summary:**
Human neural stem/progenitor cells (hNSPCs) are good candidates for treating central nervous system (CNS) injuries since these cells make beneficial factors and form mature CNS cells. However, a problem with using these cells for treatments is that many cells die after transplantation. This cell death can be lessened by inclusion of a material scaffold with the cells at the time of transplantation. Therefore, identification of optimal scaffolds for hNSPCs is a critical research focus. We investigated the properties of fibrin-based scaffolds and their effects on hNSPCs and found that fibrin generated from salmon stimulates greater hNSPC growth than mammalian fibrin. Fibrin scaffolds break down over the course of a few days after transplant, so we sought to develop a novel scaffold that would retain the advantages of fibrin but break down more slowly to provide longer support for hNSPCs. We found combination scaffolds of salmon fibrin with other molecules (hyaluronic acid and laminin) polymerize more effectively than fibrin alone and generate soft hydrogels matching the physical properties of brain tissue. Furthermore, combination scaffolds support hNSPC growth and formation of mature cells while significantly decreasing the breakdown seen with fibrin alone. HNSPCs express two fibrinogen-binding integrins, alphaVbeta1 and alpha5beta1, and several laminin binding integrins (alpha7beta1, alpha6beta1, alpha3beta1) that can bind to the scaffold. Lastly, to test the ability of scaffolds to support the formation of blood vessels necessary to provide nutrients to transplanted hNSPCs, we analyzed vessel forming endothelial cells alone and together with hNSPCs and found better vessel formation when both cell types were present in combination scaffolds. Overall, combination scaffolds of fibrin, HA, and laminin are excellent biomaterials for hNSPCs. STATEMENT OF SIGNIFICANCE: Interest has increased recently in the development of materials as neural stem cell transplantation scaffolds to treat central nervous system (CNS) injury since scaffolds improve survival of transplanted cells. We report here on a novel combination scaffold composed of 3 materials (fibrin, hyaluronic acid, and laminin) to support human neural stem/progenitor cells (hNSPCs). This combined scaffold has appropriate physical properties for hNSPCs and the CNS, supports hNSPC growth and formation of mature cells, and decreases scaffold breakdown. The hNSPCs and scaffold components work together to encourage new blood vessel formation, which will be important to provide nutrients to transplanted cells. This work marks the first report of a combination scaffold supporting human neural and blood vessel cells to encourage blood vessel formation, and sets a benchmark for materials to treat CNS injury.

**Scientific Abstract:**
UNLABELLED: Human neural stem/progenitor cells (hNSPCs) are good candidates for treating central nervous system (CNS) trauma since they secrete beneficial trophic factors and differentiate into mature CNS cells; however, many cells die after transplantation. This cell death can be ameliorated by inclusion of a biomaterial scaffold, making identification of optimal scaffolds for hNSPCs a critical research focus. We investigated the properties of fibrin-based scaffolds and their effects on hNSPCs and found that fibrin generated from salmon fibrinogen and thrombin stimulates greater hNSPC proliferation than mammalian fibrin. Fibrin scaffolds degrade over the course of a few days in vivo, so we sought to develop a novel scaffold that would retain the beneficial properties of fibrin but degrade more slowly to provide longer support for hNSPCs. We found combination scaffolds of salmon fibrin with interpenetrating networks (IPNs) of hyaluronic acid (HA) with and without laminin polymerize more effectively than fibrin alone and generate compliant hydrogels matching the physical properties of brain tissue. Furthermore, combination scaffolds support hNSPC proliferation and differentiation while significantly attenuating the cell-mediated degradation seen with fibrin alone. HNSPCs express two fibrinogen-binding integrins, alphaVbeta1 and alpha5beta1, and several laminin binding integrins (alpha7beta1, alpha6beta1, alpha3beta1) that can mediate interaction with the scaffold. Lastly, to test the ability of scaffolds to support vascularization, we analyzed human cord blood-derived

endothelial cells alone and in co-culture with hNSPCs and found enhanced vessel formation and complexity in co-cultures within combination scaffolds. Overall, combination scaffolds of fibrin, HA, and laminin are excellent biomaterials for hNSPCs. STATEMENT OF SIGNIFICANCE: Interest has increased recently in the development of biomaterials as neural stem cell transplantation scaffolds to treat central nervous system (CNS) injury since scaffolds improve survival and integration of transplanted cells. We report here on a novel combination scaffold composed of fibrin, hyaluronic acid, and laminin to support human neural stem/progenitor cell (hNSPC) function. This combined biomaterial scaffold has appropriate physical properties for hNSPCs and the CNS, supports hNSPC proliferation and differentiation, and attenuates rapid cell-mediated scaffold degradation. The hNSPCs and scaffold components synergistically encourage new vessel formation from human endothelial cells. This work marks the first report of a combination scaffold supporting human neural and vascular cells to encourage vasculogenesis, and sets a benchmark for biomaterials to treat CNS injury.

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